Protocol Article

Face masks for the prevention of COVID-19 - Rationale and design of the randomised controlled trial DANMASK-19

Henning Bundgaard[1], Johan Skov Bundgaard[1], Daniel Emil Tadeusz Raaschou-Pedersen[1], Anton Friis Mariager[1], Natasja Schytte[1], Christian von Buchwald[2], Tobias Todsen[2, 3], Kerstin Skovgaard[4], Romona Trebbien[5], Mikkel Porsborg Andersen[6], Thomas Benfield[7], Henrik Ullum[8], Christian Torp-Pedersen[6] & Kasper Iversen[9,10]

1) Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, 2) Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, 3) Copenhagen Academy for Medical Education and Simulation, Copenhagen University Hospital, Rigshospitalet, Copenhagen, 4) Department of Biotechnology and Biomedicine, Technical University of Denmark, 5) National Influenza Center, Virological Surveillance and Research, Department of Virus and Microbiological Special Diagnostics, SSI, Copenhagen, 6) Department of Cardiology and Clinical Research, Nordsjaellands Hospital, Hillerød, 7) Center of Research & Disruption of Infectious Diseases (CREDID), Department of Infectious Diseases, Copenhagen University Hospital, Amager and Hvidovre, Hvidovre, Denmark, 8) Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, 9) Department of Cardiology, Copenhagen University Hospital, Herlev-Gentofte Hospital, Denmark, 10) Department of Emergency Medicine, Copenhagen University Hospital, Herlev and Gentofte Hospital, Herlev, Denmark

ABSTRACT

INTRODUCTION
The coronavirus disease 19 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), progresses globally, and means to reduce the transmission are needed. In the community, the use of face masks is increasing world-wide, but documentation for the efficacy of this remedy is lacking. This trial investigates whether the use of face masks in the community will reduce wearers' risk of SARS-CoV-2 infection.

METHODS
This study will be a two-arm, unblinded, randomised controlled trial. We will include adults (>18 years of age) without prior confirmed COVID-19 or symptoms suggestive of COVID-19, who spend more than three hours per day outside the home with exposure to other people. A total of 6,000 participants are randomly assigned 1:1 to use face masks or not for a 30-day period during the pandemic. Participants will perform self-testing; quick test for SARS-CoV-2 antibodies (immunoglobulin M (IgM) and immunoglobulin G (IgG)) (the Livzon lateral flow test) and oropharyngeal/nasal swabs for viral detection using polymerase chain reaction (PCR). The primary endpoint following the 30-day study period is the difference in the number of SARS-CoV-2-infected individuals between the two study groups as assessed by a positive nasopharyngeal swap, a positive antibody test or a hospital-based diagnosis of SARS-CoV-2 infection.

CONCLUSIONS
We will study whether a face mask protects the wearer of the mask against SARS-CoV-2 infection. The findings are expected to apply to the present pandemic and to future viral outbreaks and to provide evidence for authority recommendations across the world.

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During the present corona-virus disease 2019 (COVID-19) pandemic with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the use of face masks has been suggested as a potential tool to limit the COVID-19 pandemic following the initial outbreak in China [1]. However, documentation for efficacy of protection in the community setting is lacking.

The primary transmission route of SARS-CoV-2 infection is thought to be through the mouth via respiratory droplets or perhaps even through aerosols containing the virus [2]. From the mouth, the virus may spread to both the airways and the intestinal canal. Moreover, it is known that SARS-CoV-2 can survive on surfaces for up to 72 hours [2]. Touching a contaminated surface may therefore be a route of transmission to the mouth or nose via the hand. A study of 26 medical students showed that they touched their face on average 23 times per hour. Furthermore, of all their facial touches, 44% involved contact with a mucous membrane [3]. A Japanese questionnaire study reported a 15% risk reduction of influenza infection when wearing a face mask [4].

Currently, face masks are used in accordance with advice by national authorities, leading to discrepancy in their use across the world [5]. A major health authority like the Centers for Disease and Control Prevention (CDC) in the United States recommends face covering in the community when social distancing is difficult to maintain [6], whereas in their guidance (5 June 2020) the World Health Organization (WHO) recommends that symptomatic individuals use face masks in order to prevent transmitting SARS-CoV-2 to others (source control). However, the WHO acknowledges that evidence supporting the protection afforded for healthy individuals from wearing a face mask is limited [7].

Danish Health Authorities recommend that healthcare staff use face masks when examining patients suspected of COVID-19 and when handling confirmed cases. The use of face mask in the community is not currently recommended in Denmark due to lack of evidence, and therefore use of a face mask outside hospitals is uncommon in Denmark.

The evidence for the efficacy of face masks for healthcare workers is compelling [8]. A recent and widely quoted systematic review of observational studies published in the Lancet found that use of face masks more than halved the risk of SARS, MERS and/COVID-19 infection. However, the association was stronger in the healthcare setting (including 26 studies) than in the non-healthcare setting (including three studies) [9]. Several challenges are linked to wearing disposable face masks in the community, including practical aspects such as potentially incorrect wearing, reduced compliance, reduced durability of the mask depending on type of work, weather, etc. Such circumstances may make is necessary to shift the mask during the day. Wearing a face mask may be physically unpleasant, and there may also be psychological barriers to wearing a mask. Additionally, the wearer of a face mask may change to a less cautious behaviour due to a sense of safety as pointed out by the WHO. Furthermore, the eyes of individuals carrying a face masks are not covered. Such challenges may reduce the efficacy of the face mask to avoid viral infection. These concerns may partially explain that health authorities around the world have different recommendations on the use of face masks [10]. Due to the current lack of evidence, Shou Feng et al. concluded in the above-mentioned Lancet paper that "Universal use of face masks could be considered if supplies permit. In parallel, urgent research on the duration of protection of face masks, the measures to prolong life of disposable masks, and the invention on reusable masks should be encouraged" [10].

Face masks can be made by different materials and have various designs, e.g. N95 masks, surgical face masks and homemade masks [11]. A study comparing surgical face masks and homemade masks found that both masks significantly reduced the number of microorganisms. However, the surgical mask was three times more effective in blocking transmission [12]. N95 masks (respirators) and surgical face masks are expected to have almost similar effectiveness for healthcare workers based on protection against infection with influenza virus [13]. A recent systematic review and meta-analysis investigated the

effectiveness of N95 respirators versus surgical masks [14]. The authors concluded that N95 respirators compared with surgical masks are not associated with a reduced risk of laboratory-confirmed influenza, and they suggested that N95 respirators should be reserved for high-risk medical staff [14]. Similar results have been found in other studies [15, 16].

Surgical face masks may therefore be effective against COVID-19 transmission [17-19]. Thus, face masks can probably protect against virus infection by reducing the risk that virus enters the mouth or nose via respiratory droplets or aerosols. Additionally, it is likely that face masks may reduce the risk of transmission by reducing face-touching with virus-contaminated fingers and hands.

Given the present knowledge, it must be expected that a considerable proportion of the world's population will be infected with SARS-CoV-2, and a substantial proportion will develop COVID-19. During the early phase of the COVID-19 pandemic, it was estimated that approximately 10% of the Danish populations, equivalent to 600,000 Danes, would contract COVID-19 during the current first wave of the pandemic. It is assumed that several waves of COVID-19 will occur. In Denmark, the epidemic has been expected to peak in April.

The aim of the Danish trial of face masks for the prevention of COVID-19 (DANMASK-19) in the community is to assess whether face masks reduce the wearer's risk of transmission with SARS-CoV-2.

METHODS

The study is a two-arm, unblinded, randomised controlled trial with Danish nationwide inclusion.

The protocol is registered with clinicaltrials.gov (Trial identifier NCT04337541) and adheres to the recommendations for trials described in the SPIRIT Checklist.

Eligibility criteria

Inclusion criteria are adults (above 18 years of age) who are not recommended wearing face masks at work according to Danish authorities, working out-of-home with exposure to other people for more than three hours per day and who have not previously been infected with COVID-19 (Table 1).

TABLE 1 / Inclusion and exclusion criteria in the DANMASK trial.

| Criteria	Description
Inclusion criteria	Older than 18 years of age and without symptoms associated with SARS-CoV-2 Working out-of-home with exposure to other people for more than three hours per day Does not normally wear a face mask for daily work
Exclusion criteria	Previously tested positive for SARS-CoV-2 Has had a fever in the past month

Randomisation and blinding

Participants will be enrolled through RedCap Software (Tennessee, USA) according to formally self-reported inclusion and exclusion criteria and will then be randomised. Randomisation is conducted by a computer algorithm and stratified by region. Physicians, participants and study personnel responsible for data management are not blinded as this trial has an unblinded design.

Interventions

Participants will be randomly assigned 1:1 to recommended to follow the authorities general COVID-19 precautions or recommended to follow the authorities' general COVID-19 precautions and wearing face mask for a 30-day period (Figure 1). Both groups are encouraged by the study group to follow the authorities' updated COVID-19-related recommendations during the study period.

FIGURE 1 / Timeline for participants randomised to face mask (group A) and for controls (group B). The data collection time points and duration of the trial are indicated.
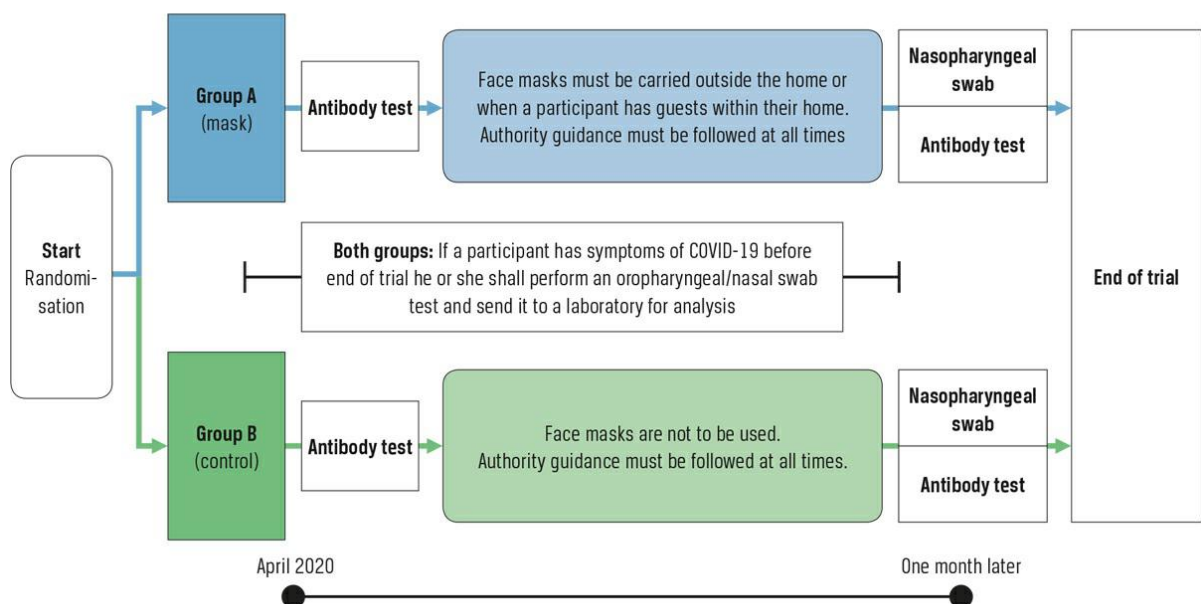
Following randomisation, participants will receive a package with all relevant equipment at their address. All participants will receive COVID-19 immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody test kits (Lateral flow test, Zhuhai Livzon Diagnostics Inc., Guangdong, China), oropharyngeal/nasal swab kits (Zymo Collection Swab, Zymo Research, Irvine, CA, USA) and detailed written instructions along with a help-line phone number. Participants randomised to wearing face masks will additionally receive 50 surgical face masks with ear-loops (Type II, EN 14683, ABENA, Aabenraa, Denmark, made in CN) equivalent to a month's usage.

Guided by the written material and video instructions, all participants will conduct antibody (IgM and IgG) testing at day 0 and day 30 in addition to a nasopharyngeal swab at day 30 as well as during the period if symptoms of COVID-19 develop. At all time during the study period, participants can call a hotline with medical expertise and guidance. During the period, we will collect information from the participants through surveys on an almost weekly basis. The surveys are also intended to assess and improve compliance. If the participants develop symptoms during the study, they will self-register their symptoms in the online RedCap survey and perform oropharyngeal and nasal swabs and send these by currier to the hospital for analysis. In these cases, the participant is also encouraged to contact his or her general practitioner or the local hospital.

Guidance on swabbing and antibody testing

Participants will be guided by both written and video instruction (Figure 2). Video instruction material was created specifically for this trial. Antibody testing results will be collected through the survey. In addition, participants will be asked to take photos of the test in order for us to clarify if uncertainty of test results occurs. The swab tests will be sent from the participant to the laboratory shortly after the procedure. Guidance on the use of face masks are in accordance with WHO recommendations [4]. Participants in the face mask arm are instructed in consistent use of surgical face masks outside of their home.

FIGURE 2 / The video instruction of (A) swab and (B) antibody testing developed specifically for this trial and distributed to the participants via e-mail and QR code on delivered material.
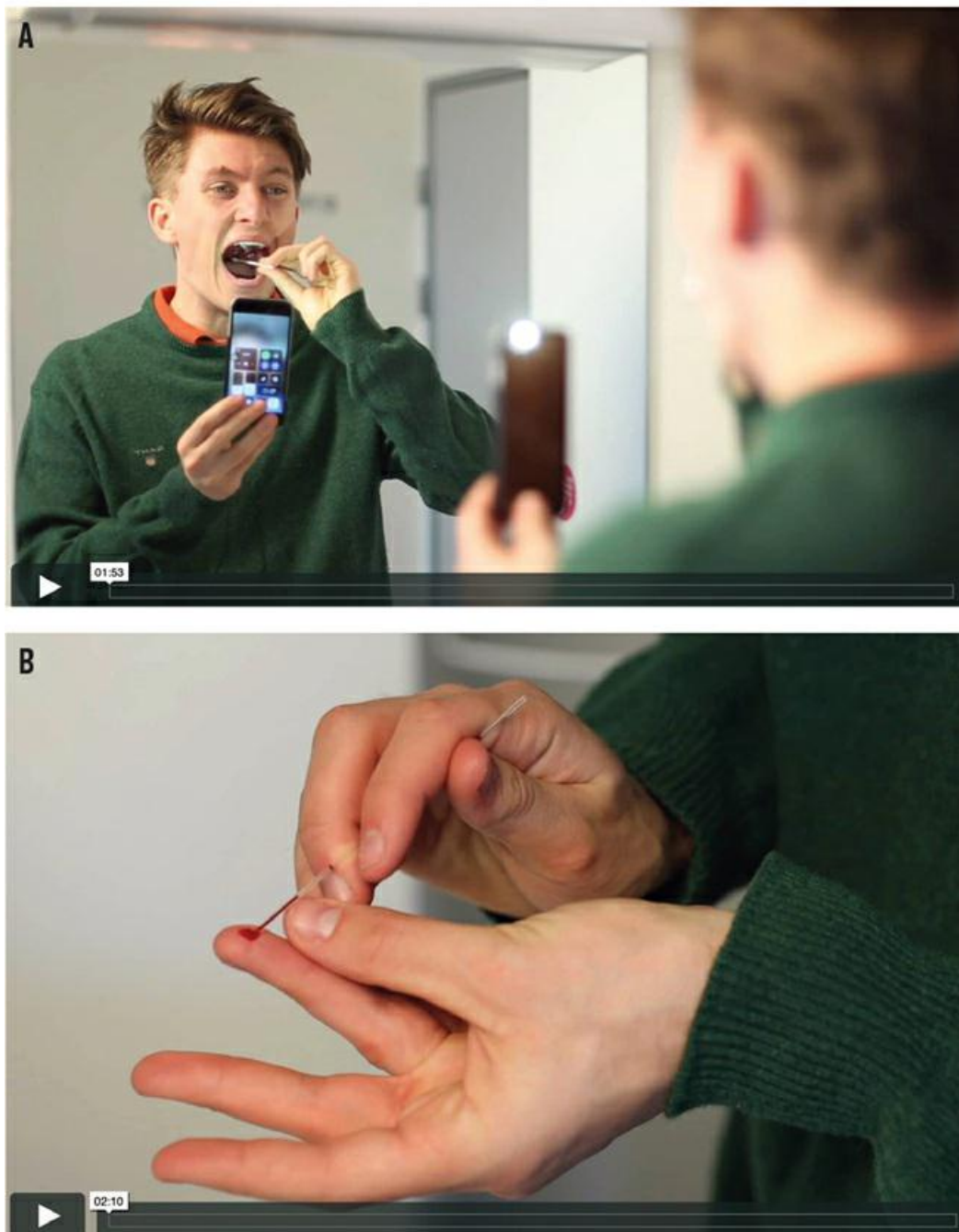
Endpoints

The primary endpoint following the 30-day study period is the difference in the number of infected individuals between the two study groups as assessed by a combined endpoint

consisting of A) a positive oropharyngeal/nasal swab for SARS-CoV-2 (PCR) and/or B) an antibody test; development of a positive SARS-CoV-2 antibody test (IgM and/or IgG) during the study period and/or C) SARS-CoV-2 infection diagnosed in a hospital/healthcare facility.

Secondary endpoints include other respiratory viral infections including para-influenza-virus type 1, para-influenza-virus type 2, human coronavirus 229E, human coronavirus OC43, human coronavirus NL63, human coronavirus HKU1, respiratory syncytial-virus A, respiratory syncytial-virus B, influenza A virus or influenza B virus at the end of the study period between groups. A full list of tertiary endpoints can be found using the ClinicalTrials.gov Identifier: NCT04337541.

Statistics

Power calculations were conducted with an expected 2% incidence of COVID-19 during the study period; by inclusion of a total of 4,636 participants, an expected reduction of the risk to 1% by wearing face masks can be demonstrated with a power of 80% and a two-sided p-value of 5%. With an expected 20% fallout, a total of 6,000 participants will be included. For the statistical analysis, baseline categorical variables will be presented as numbers and percentages for categorical variables and mean (SD) or median (IQR) for continuous variables, as appropriate. Differences in baseline characteristics will be compared with the chi-squared test for categorical variables and the two-sided t-test or rank sum test for continuous variables, as appropriate. Cumulative incident figures for outcome will be compared by the face mask group and the control group. The level of statistical significance is $p < 0.05$.

Participant selection and inclusion period

Recruitment of participants will be done by advertising in local and national media to individuals and to private companies and public organisations. Individuals interested in participating get access to detailed project information via a link from the hospital's website. Through this information, they have access to project staff in case of questions or need of further information. If the individual decides to participate, he or she registers in RedCap Software (Tennessee, USA) through the same link and answers a survey. Inclusion will be done throughout April 2020.

Data-sharing statement

Following de-identification, published participant data will be shared upon request from researchers who provide a sound proposal. This includes data sharing to methodologically sound meta-analysis studies. Study protocol and participant information will be available upon request. Data will be available beginning nine months and ending five years after publication. Proposals should be directed to the corresponding author.

Ethics and data management

All data will be collected through questionnaires and analyses of the oropharyngeal and nasal swabs. Data will be managed in RedCap and all participants will give informed consent prior to enrolment.

The study was registered with the Danish Data Protection Authorities (record number: P-2020-311). The study was presented to the regional scientific ethics committee of the Capital Region. The committee concluded that the study did not require a scientific ethics approval. Information about study subjects will be kept confidential according to Danish law.

DISCUSSION

The study is expected to provide evidence on whether authorities worldwide should recommend the use of face masks in the general community as a tool to impede transmission of COVID-19. If proven effective, the use of face masks has the potential to significantly contribute to reducing the spread of COVID-19 and open societies earlier. Oppositely, if proven ineffective, the current use of face masks in the general public in multiple countries is not justified. The findings from this research should contribute to the evidence of protection of face masks during this pandemic as well as future viral epidemics and pandemics and thereby guide authorities across the world.

LITERATURE

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